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RECENT ADVANCES IN OUR KNOWLEDGE OF SLEEPING SICKNESS.

No. 2.

BY

ARTHUR G. BAGSHAWE, M.B., D.P.H. (Cantab.)



(Paper read at a Meeting of the Society of Tropical Medicine and Hygiene, Friday, October 21st, 1910).

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It is just a year since I had the honour of addressing you on this subject. During this period though no remarkable discoveries, such as that of the permanent infectibility of tsetse-flies, have been made, there has been progress in most directions, notably in our knowledge of the method and conditions of transmission.

ÆTIOLOGY.

Do biting flies other than Glossina carry Trypanosoma gambiense?
—At our meeting in 1909 we had to consider the belief of the members of the French Commission that biting insects other than tsetse, for example mosquitoes, spread sleeping sickness. In the period under review no cases in which this was suspected have been put on record. An important piece of negative evidence has, however, come to hand.¹ The Islands of Principe and San Thomé lie a few miles apart in the Gulf of Guinea. They have a similar population, similar vegetation, the same

climate. Principe contains tsetse-flies, San Thomé does not. On Principe there is much sleeping sickness; of nearly 2,000 persons examined by the Portuguese Commission 23·5 per cent. were found to be infected. On San Thomé, though three months were spent there, the members of the Commission were unable to find a single case; and this was not due to want of opportunity, for cases of sleeping sickness are frequently imported into each island. On San Thomé moreover they found all the blood-sucking insects which they had seen on Principe, with one exception, the genus *Glossina*. This is to my mind presumptive evidence that in nature transmission of sleeping sickness occurs only exceptionally, if at all, in the absence of tsetse-flies. It confirms the old observations in the West Indies and on the American Continent, and supports the belief that sleeping sickness will never spread in a country where there are no tsetse.

Do species of Glossina other than palpalis carry Trypanosoma gambiense?—Can we still adhere to the belief that among the tsetses the species *palpalis* is the only carrier? Until quite recently it appeared that we could. No one could point to an undoubted case of infection by a tsetse other than *palpalis*; and in districts like the East Africa Protectorate or the Katanga, where, owing to the number and ubiquity of the tsetse-flies, the disease might be expected to spread, it has not in fact done so. KLEINE² reported at the end of last year an experiment on a large scale which shewed that *Glossina morsitans* was not, under the conditions of the experiment, hospitable to *Trypanosoma gambiense*. He fed 672 flies of this species, bred in his laboratory, for four days on eight monkeys infected with sleeping sickness, and thereafter on a series of seven healthy monkeys till the sixty-fifth day. Not a single animal became infected. Unfortunately, we learn from Northern Rhodesia and Nyasaland that sleeping sickness has in several cases, European as well as native, been there contracted,³ and we are practically certain that Nyasaland, if not the Zambesi and its tributaries, is outside the area of distribution of *Glossina palpalis*.* This is the first piece of unimpeachable evidence that sleeping sickness can spread in the absence of *palpalis* and it suggests

* It has been suggested that the Rhodesian disease is not sleeping sickness, *i.e.* that the trypanosome is not *gambiense*. The suggestion seems to me too speculative to merit discussion in this paper.

that another species of tsetse may be capable of acting as carrier. Recent work on the transmission of animal trypanosomes makes this not improbable. Sir DAVID BRUCE and his colleagues Captains HAMERTON, BATEMAN, and MACKIE,⁴ find that in Uganda *Glossina palpalis* can be infected in the laboratory by three different animal trypanosomes. KLEINE'S⁵ first successful experiment was made with *Glossina palpalis* and an animal trypanosome which had been introduced into his experimental animals by *Glossina morsitans*. BOUFFARD⁶ finds that a trypanosome in West Africa (*Trypanosoma cazalboui*) can be transmitted equally well by *Glossina palpalis* and *tachinoides*. BOUET and ROUBAUD⁷ confirm Bouffard and find that *Glossina longipalpis* is as effective as the other two; moreover, they have transmitted a trypanosome of *dimorphon* type by means of *Glossina longipalpis* and *tachinoides* as well as by *Glossina palpalis*. (All these are instances of transmission after a non-infective period.) Is it not at least reasonable to suppose that *Trypanosoma gambiense* also may be transmitted by more than one species of *Glossina*? It is worth noting that though Kleine's experiment with *Glossina morsitans* and *Trypanosoma gambiense* was negative, his colleague TAUTE found, as late as the fortieth day, developmental forms of the parasites in the gut of two flies; a finding which suggests that under other conditions the development might be completed.

But if sleeping sickness is really being diffused in Rhodesia by tsetse-flies other than *palpalis*, why has the disease not spread in East Africa by the agency of *Glossina pallidipes* and *fusca*, or on the high ground in the Katanga by that of *Glossina morsitans*? I suggest as a provisional hypothesis that it is because on these uplands the air is too cool and too dry to admit of the parasite's completing its development in the body of the insect. There is abundant analogy for this. It is, I believe, well known that certain ticks harmless on high ground become bearers of disease when they are brought into valleys. In malarial mosquitoes development takes place more and more slowly as the temperature falls, till at a certain point it ceases to be completed. The same reason may account for the disappearance of yellow fever with the advent of cold weather. On Lake Nyasa, on the other hand, and in the Luangwa valley in North-Eastern Rhodesia the altitude is low; the air is warmer as well as moister than at higher levels; and it is conceivable that the tsetse-flies there present (*fusca* and *morsitans*) are taking the rôle played by

palpalis in other parts of Tropical Africa. There is some evidence that *Glossina morsitans* occurs in this part of Africa under conditions somewhat similar to those of *palpalis*. Thus MASTER describes *morsitans* on a river flowing into Lake Mweru as settling on the overhanging boughs and behaving in every respect like *palpalis*. No specimens of the latter species were found.

To the suggestion that *Glossina morsitans* may be responsible for these infections it may be objected that the cases are few and scattered, whereas the disease should spread rapidly in places where a carrier is so abundant and so bloodthirsty. A little consideration will, however, show that this need not be so. In the laboratory it has not been found possible to infect more than five per cent. of *palpalis*, and the infection rate in nature has not been shown to reach such a high level; the average in many experiments was 2·5 per thousand. It is also quite conceivable that *Glossina palpalis* may be more susceptible to infection than the other species of tsetse. Again, sleeping sickness appears to have spread very slowly in some areas where *palpalis* was abundant, and in every case the disease has probably been long in establishing its footing. KINGHORN and MONTGOMERY⁸ write:—

It is very surprising to notice, even in the case of *Gl. palpalis*, the slow rate at which the disease spreads under the most favourable circumstances. In two or three villages on Lake Tanganyika where this fly, as well as *Gl. morsitans*, was caught in the gardens, and into which the disease, in all probability, was introduced four or five years ago, only nine or ten cases were found; and if this is so, it is quite conceivable that the rate of spread, in the event of *Gl. morsitans* being an *active* transmitter, as opposed to a *mechanical* one, would be much slower.

It is to be hoped that the cause of these extra-*palpalis* infections will soon be demonstrated. Investigations by skilled and well-equipped workers should be promptly undertaken; for the mere suspicion that *palpalis* may owe its bad reputation to its habits and habitat rather than to any differences which may exist between it and the other species would cause a feeling of insecurity in all parts of South Africa where tsetse-flies are found. The fact, however, that not till seven years after the discovery of the association between *palpalis* and sleeping sickness has undoubted evidence of transmission in the absence of *palpalis* come to light, suggests that only rarely are the necessary conditions fulfilled in the case of *morsitans*, *fusca*, and the rest, and that we are still justified in regarding *Glossina palpalis* as *the* transmitter.

It may be pointed out here that, if it should be proved that *Glossina morsitans* or *fuscus* under certain conditions in nature transmit *Trypanosoma gambiense*, it may be taken as certain that *Glossina tachinoides* can do the like. This would affect chiefly Northern Nigeria: for there *tachinoides* appears to exist alone in large numbers under precisely the same conditions as *palpalis* elsewhere, *i.e.*, along rivers and watercourses near which man lives and which he must visit. At present, as far as we know, these parts are free from sleeping sickness.

Natural transmission by Glossina palpalis.—Since KLEINE opened a new road to investigators by showing that tsetse-flies could, after a latent interval, be permanently infected with pathogenic trypanosomes, our knowledge of this subject has grown, but it cannot be said that it has reached finality. That such late development is the rule in the insects which transmit trypanosomes from mammal to mammal seems probable. BOUFFARD⁶ has demonstrated it for *Trypanosoma cazalboui* and *Glossina palpalis* and *tachinoides*; BRUCE⁴ and his colleagues for *Trypanosoma vivax* (perhaps the same as *cazalboui*) and *Glossina palpalis*; and MINCHIN and THOMSON⁹ for the rat trypanosome and rat flea. Moreover, there is little evidence that direct transmission ever occurs. BRUCE¹⁰ and his co-workers experimented to find out the part played by direct transmission. A cage containing laboratory-bred flies (*Glossina palpalis*) was placed for some little time on an animal infected with *Trypanosoma gambiense*, then suddenly transferred to the healthy animal, and so backwards and forwards for ten or fifteen minutes. In this way a goat and a monkey were infected from monkeys. Similar experiments with the ox serving as infected animal failed; which may be easily explained by the scarcity of *Trypanosoma gambiense* in bovine blood. When there was an interval of half an hour to forty-eight hours between the feeds not a single case of infection occurred. In this series of experiments 472 flies in all were used in ten trials and the feeding was continued for eleven to fifteen days, so that the possibility of transmission was thoroughly tested. The result makes it fairly certain, as Sir DAVID BRUCE points out, that the successes of the former Sleeping Sickness Commission, after twenty-four and forty-eight hours as it was supposed, were the result of late development, the same flies having been used throughout. The conclusion is that mechanical, or direct, transmission plays a small part, if any, in the spread of sleeping sickness.

KLEINE² too obtained no evidence for direct transmission after an interval. He fed 1,910 tsetse-flies on infected animals, and eighteen to twenty-four hours later on healthy animals; there was no instance of transmission. We may, I think, conclude that direct transmission by any agency is a rare event, and that, though it may account for individual cases of infection, it should not be called in to explain an epidemic. Only that insect, in fact, which is hospitable to *Trypanosoma gambiense*, and capable of becoming permanently infected by it, is of moment in the extension of the disease. Consequently, if sleeping sickness spreads in any district it is fairly certain that a true host is to be found there.

When the development of the trypanosome in the fly was discovered, the non-infective interval appeared to be a definite fixed period. A long series of experiments carried out by the *Sleeping Sickness Commission⁴ seems to demonstrate that it may be very variable. Both wild and bred flies were used. The experimental animals were monkeys. In seven positive experiments with wild flies the shortest time which elapsed before a fly became infective was eighteen days, the longest was forty-five, and the average thirty-two. With the laboratory-bred flies, which are more difficult to infect, these periods were longer, the average being thirty-six days. In neither series was it found easy to infect the flies; in one of the first 350 were used without result; they were fed on healthy monkeys for 66 days without producing infection, and the fifteen which remained at the end of the experiment contained no flagellates. As a result of all the experiments, it was concluded that *Trypanosoma gambiense* multiplies in the gut of about one in every twenty *Glossina palpalis* which have fed on an infected animal. This is the same proportion as was obtained by KLEINE.¹¹ There is no reason to suppose it is ever as high in nature; for from the recorded transmission experiments it has been deduced that not more than 2·5 per 1,000 flies are infected in natural conditions, 11 per 1,000 being the highest in any experiment. Why is the proportion of infectible flies so small? Is it that the trypanosomes are as a rule unable to maintain themselves or at least to multiply in the intestine, or are they

*The Sleeping Sickness Commission of the Royal Society was in Uganda from 1908-1910. As the "Sleeping Sickness Commission" it is frequently referred to in this paper. Its members were Colonel Sir David BRUCE, F.R.S.; Captains HAMERTON and BATEMAN, R.A.M.C., and Captain MACKIE, I.M.S.

in many instances devoured by phagocytes under the new conditions, or are many tsetses naturally immune to the infection? It does not appear that a higher proportion becomes infected when a batch of flies is fed for a long period on the infected animal. Sir DAVID BRUCE¹² believes that it is a case of survival of the fittest; in a few flies a few hardy parasites not only survive, but reproduce their kind, and in course of time become capable of infecting a new vertebrate.

In the case of an animal trypanosome (*Trypanosoma cazalbowi* or *vivax*) which undergoes all its development in the fluid contained in the proboscis, the percentage of successful infections is much higher. In BOUFFARD'S⁶ experiment it varied between 11 and 70; in those of the Sleeping Sickness Commission⁴ 17 per cent. were infected, *i.e.*, more than three times as many as were infected by *Trypanosoma gambiense*. This suggests that the intestine affords a less favourable medium than the proboscis.

There is evidence that *Trypanosoma gambiense* may multiply in the fly without becoming infective. In six experiments of the Sleeping Sickness Commission with bred flies, in which the flies that remained to the end were killed and dissected, some were found containing flagellates. These must have been *Trypanosoma gambiense*, but they had not transmitted the disease in biting, nor did their introduction into healthy monkeys produce infection. In other instances the injection of infected flies or of fluid from the alimentary canal into susceptible monkeys produced sleeping sickness. The infected flies remained capable of transmitting the disease till their death, which in the longest-lived was on the seventy-fifth day.

We are still in the dark as to what goes on in the insect during the non-infective period. The fact that the trypanosomes in the alimentary canal are infective goes to show that there is no invasion of the body fluids and afterwards of the salivary glands, such as CHAGAS¹³ observed in the case of *Schizotrypanum*. There is no evidence that *Trypanosoma gambiense* is infective to the tsetse-fly at any one stage of its life history more than another.

No observer has obtained any evidence of germinal infection. There seems to be no such thing as hereditary transmission in the fly of those trypanosomes which are pathogenic to mammals. KLEINE'S observations concerned 1,527 flies, BRUCE'S nearly 1,700. In their experiments with

bred flies no case of infection occurred before the eighteenth day, and that only with flies previously fed on an infected animal.

Reservoir Hosts of Trypanosoma gambiense.—Perhaps the most striking discovery in the period under review was that of BRUCE¹⁴ and his colleagues in Uganda, that the flies caught on the shore of the Victoria Nyanza, cleared of inhabitants for some two years, were able to infect monkeys with sleeping sickness. Administrators had nursed the hope that the flies, compelled to feed on the lake shore vertebrates rather than man, would soon lose their infectivity and then it would be possible, they supposed, to plant the same or a different population on the shore without risk. This would in any case have been a dangerous step in view of the difficulty of discovering infected persons, but now the idea must be quite given up. Various causes of this continued infectivity were suggested, and naturally attention was specially turned to the possibility that some wild animal might be the source of the infection. Hitherto little evidence had been obtained. GREIG¹⁵ had found an epidemic of what was believed to be sleeping sickness in dogs, and KOCH¹⁶ had reported the finding of a naturally infected monkey. The Sleeping Sickness Commission¹⁷ took up the matter again. They had previously found, as had KLEINE, that cattle could be infected with the human trypanosome, and Kleine had pointed out that such infection was produced much more readily by the bites of flies than by artificial inoculation. The members of the Commission decided that, if cattle could be shown to act as a reservoir, the wild antelopes on the lake shore might reasonably be suspected also. They carried out a series of transmission experiments with *G. palpalis* and succeeded in infecting monkeys and goats from cattle. Many cattle were examined to see if they harboured *Trypanosoma gambiense* naturally; an infected cow was found in one of the islands. It was thus proved that cattle are able to act as a reservoir. More recently Sir DAVID BRUCE¹⁸ has written:—

It has also been proved by direct experiment that the antelope, such as the water-buck and bush-buck, are just as capable as the cattle of being infected with sleeping sickness. In several experiments infected flies have been fed on antelope; in ten days or so, when the parasites appeared in their blood, laboratory-bred flies have been fed upon them, and finally, after some thirty days, these laboratory-bred flies have been fed on monkeys, and the monkeys have in their turn become infected.

After recalling that the injection of the blood of antelopes, as well as

of other wild animals, into susceptible animals has always had a negative result he adds :—

The opinion is growing in my mind that it is more than probable that the wild game on the lake shore will be found to act as a reservoir.

If, indeed, it is definitely proved that wild animals form a reservoir of the sleeping sickness virus, it is plain that all places where such animals and the sleeping sickness fly co-exist will be uninhabitable by man till the circle is broken by the extermination of either the vertebrate or the invertebrate host. The “tsetse-fly and big game” may become a burning question in human as well as in animal pathology.

Though no cases of infection by *sexual coitus* have been recently reported, experimental work suggests that it may occur. G. MARTIN and RINGENBACH¹⁹ found that by allowing blood containing *Trypanosoma gambiense* to run into the vagina they could infect guinea-pigs.

DIAGNOSIS.

Little of importance has been published on this subject in the last year. It is now, I think, recognised that *gland palpation*, combined with puncture, employed in the period when occasional fever is the only symptom, and while the patient is able to pursue his ordinary vocation, will not discover even a large proportion of the infected. Wherever serious attempts are made to detect cases of trypanosomiasis the blood is examined as well as the glands. Dr. KINGHORN,²⁰ formerly a strenuous advocate of gland palpation, after finding five cases of trypanosomiasis by the blood method among 119 natives who had been previously examined by the gland method with a negative result, wrote :—

None of these five presented any marked degree of glandular enlargement, and all in every way appeared to be in the best of health. It would appear, therefore, that in these natives [Gold Coast] glandular enlargement may not be met with in a fair percentage of those infected, and that, consequently, the examination of blood preparations is of equal importance to that of the gland juice.

In forty-five cases of trypanosomiasis in whites the parasites were found in no less than thirty-two instances first in the blood, and only in six by gland puncture. This was doubtless because in many of the thirty-two the glands were not explored, but it serves to illustrate the value of blood examinations in this disease. The drawback of the blood method is that in many instances the trypanosomes are scarce. The discovery of our PRESIDENT and Dr. DAVID THOMSON²¹ that there is a

trypanosome tide once in every seven days suggests that it is advisable, in cases in which the thick-film method is not applicable, to repeat blood examination daily for at least a week so as to include the period of flood. Whether the thick film or the more usual technique of blood examination should be used depends on the skill of the observer; to the novice or the unpractised eye the former presents difficulties.

More observations have been recorded on *auto-agglutination*, but we do not yet know the cause of the phenomenon. TODD²² found that it was at its maximum just after trypanosomes had been numerous in the blood; if this is generally so, the curve of auto-agglutination may follow that of periodicity. TODD has published a table showing the proportion of cases in which trypanosomes and auto-agglutination respectively were found in 1,406 persons examined on a single occasion in the Congo State. It shows that, while auto-agglutination may be absent when trypanosomes are present, of cases in which the corpuscles clumped a large proportion harboured trypanosomes: thus, when agglutination was present, 183 persons had trypanosomes and 212 had not; when it was absent, the figures are 24 and 987. The association of this phenomenon and trypanosome infection in man is thus well shown. It remains, therefore, true that well-marked clumping of the red corpuscles, in a person who has visited or resided in an infected area, is a phenomenon which should lead the observer to make repeated search for trypanosomes.

A study of the published *leucocyte counts*, especially in Europeans, shows that in trypanosomiasis lymphocytosis nearly always occurs, and that the increase is chiefly at the expense of the polymorphonuclears. The same has been noted in monkeys infected with *Trypanosoma gambiense* (BENTMANN and GÜNTHER).²³ If in a doubtful case this altered relation were demonstrated, it would go to support the diagnosis of trypanosomiasis, but it must be remarked that such an altered relation has been recorded, apart from disease, in whites long resident in the tropics.

While there is a general likeness in the *symptoms* in the recorded cases of trypanosomiasis, one hears now and again of a case in which none of the characteristic signs was present, *e.g.*, one recorded by Dr. HEARSEY,²⁴ in which there was severe headache and an oscillating temperature; the patient was able to work; death occurred with the disease undiagnosed

in the sixth week. The nature of the illness was revealed when blood smears taken during life were afterwards examined. Such cases are probably not rare. Severe headache seems almost characteristic of *Trypanosoma gambiense* infection in man.

The discovery of the trypanosome in one or other of the body fluids remains the only certain means of unmasking a trypanosome infection.

SYMPTOMS.

In a disease so long known as sleeping sickness it is not to be expected that much in the semeiology would be now unrecorded. THIROUX²⁵ has described skin lesions which he believes are those of trypanosomiasis. These consist of papules, scattered or in patches, and in some cases ulcerated. They have not been seen in Europeans and there is at least a doubt whether they are really due to trypanosomiasis. MORAX²⁶ has described a case of choroidoretinitis which he believes was the result of trypanosome infection. He had examined the fundi two years earlier and found them normal, and he was able to exclude syphilis since the Wasserman reaction was negative. The choroidoretinitis came on at the same time as cyclitis which is a recognised symptom in sleeping sickness. Van SOMEREN²⁷ believes that lesions of the optic nerve may occur in sleeping sickness apart from treatment by organic arsenicals, and the same opinion has been expressed by Ayres KOPKE.²⁸ Such changes might not influence the vision but would certainly predispose to blindness a patient treated by organic arsenicals. It may be noted that SPIELMEYER found degenerative changes in the optic nerve and tract of dogs infected with nagana.

An analysis of the symptoms in fifty published cases of sleeping sickness in Europeans has been lately published in the *Sleeping Sickness Bureau Bulletin*. According to this the most frequently recorded are, in descending order: fever, erythema, loss of strength, increased frequency of heart beat, somnolence, œdema, large spleen, anæmia, headache, and epileptiform convulsions. The relative position of symptoms in the scale depends to some extent on the proportion of advanced to early cases which did not progress. Thus if many of the cases tabulated are advanced, such symptoms as somnolence and epileptiform convulsions will rank high.

TREATMENT.

In the last twelve months no new trypanocide has come into use, unless it be aniline antimonyl tartrate. We have learned little more as to the use of the arsanilates such as atoxyl and soamin. Arsenophenylglycin promises to be superior to either, but the data are as yet incomplete.

Arsenophenylglycin.—The most favourable reports of this drug come from Togoland, where in Dr. VON RAVEN'S²⁹ hands the results are good. It must be premised, however, that sleeping sickness in Togoland seems more amenable to trypanocides than sleeping sickness on the other side of the continent. Here, in German East Africa, ECKARD had much less success, but, as he did not give the drug in the right way, we may disregard his results. VON RAVEN has followed the method insisted on by EHRLICH,³⁰ of giving one or two large doses and no more. In one series of thirteen in which these varied between 0.5 and 1.0 gm., no case had relapsed seven to eleven months later. Unfortunately, the patients are still in their native land and liable to reinfection, so that if trypanosomes reappear in them we shall be unable to say whether we have to do with a relapse or a new infection. VON RAVEN, in the same paper, gives data which show that it is not only advisable but absolutely essential to follow the guidance of EHRLICH in the administration of this drug. He finds that the quantity given is immaterial as regards the severity and even occurrence of toxic symptoms. It is the method alone that matters. These symptoms hardly occur except when injections are repeated at more or less short intervals. A quantity which, given in one dose or in two doses on consecutive days, was borne without the least disturbance, given in four or six doses spread over ten to fifteen days produced such symptoms as fever, oedema, urticaria, conjunctivitis and bronchitis, bile in the urine, jaundice, and, rarely, diarrhoea. The skin would peel off in large flakes. Two patients died rapidly from heart failure. In some instances, after the acute symptoms, the patient lost strength and flesh and eventually died. He gives the following advice as to the employment of the drug: to exclude advanced cases; to give a single injection, or two on adjacent days, of at least 0.8 to 1.0 gm.; if relapse occurs within six weeks to change the treatment. These correspond with the instructions previously given by EHRLICH.

The danger in spreading the injections over many days may be partly due to a rapidly developing sensitiveness of the tissues—to what EHRLICH describes as an alteration of the balance of distribution between host and parasite—but is partly the result of slow excretion. TENDRON³¹ found that after the injection of one gram the maximum excretion in the urine took place between the third and sixth day, and that ten days later it was not complete. FISCHER and HOPPE made similar observations with the same results.

EHRLICH³⁰ has pointed out the advantage of getting in the trypanocide when parasites are numerous in the blood. The theory is that some killed at once produce by their death antibodies, and to these the remainder succumb. The maximum *Ictus immunisatorius* is thus produced. I am not aware that this has been practised, but the principle is sound; and now that ROSS and THOMSON²¹ have demonstrated that the number of parasites may wax and wane with unfailing regularity, it should not be difficult to meet the rush of parasites with an effective dose of poison. Given at the right moment, a small quantity of a relatively inefficient parasiticide may effect more than a large dose of a powerful one, through the action of the antibodies produced.

Other trypanocides which deserve mention are *tryparosan* and *aniline antimonyl tartrate*. Tryparosan, introduced by EHRLICH, is a drug which promises to be of service. BRODEN and RODHAIN³² tried it both intravenously and by mouth; the latter method was the more effective. The blood was cleared when 4 or 5 gm. were ingested daily for two or three days, but relapses soon occurred. G. MARTIN and RINGENBACH³³ have also tried this substance; it was given by the mouth, and was afterwards found in the fluid of gland puncture. A rather larger amount than the above was needed to clear the blood and glands; relapses were not slow to occur. It is not suggested that this dye can replace the more powerful trypanocides, but that it should prove a useful adjunct. It has the great advantage, as far as natives are concerned, that it has not to be introduced through a needle.

Aniline antimonyl tartrate has been used with some apparent success by THIROUX,³⁴ who found it more effective and less toxic than the potassium salt. It was given intravenously in association with atoxyl. Three patients so treated were free from trypanosomes, as tested by the inoculation of their blood and cerebro-spinal fluid into *patas*

monkeys five months later. G. MARTIN and RINGENBACH³⁵ formed a less favourable opinion of the drug; the general state of the patients was not improved, and trypanosomes were found after treatment in the cerebro-spinal fluid.

Arsenobenzol.—Of the action of this drug, more commonly known as “606,” in sleeping sickness we have little information. EHRLICH^{35a} has recently stated that it is effective in this disease as well as in trypanosome diseases of animals. It is possible that it is superior to arsenophenylglycin. It appears to be less poisonous to the tissues.

As to the older methods, the experience of the medical officers in charge of camps in Uganda³⁶ favours a short course of atoxyl or soamin, followed by a longer one of orpiment, and Van SOMEREN has had good (temporary) results from the simultaneous use of soamin and perchloride of mercury. They did not find antimonial injections of benefit. L. MARTIN and DARRÉ,³⁷ whose experience is derived from the study of European cases, advocate atoxyl and orpiment in mild infections, atoxyl and antimony in the more severe and for Europeans. One of their patients, whom they believe cured, did not react to atoxyl, but improved rapidly with tartar emetic injections.

None of the trypanocides at present in use can be relied on to banish the parasites from the cerebro-spinal fluid.

The action of the arsanilates, or the arylarsonates as they are often called, on the eye has been studied by IGERSEIMER.³⁸ He experimented on several species of animals, and concluded that atoxyl has a selective action on the nerve cells of the eye, and that the point of attack may be central or peripheral, or may lie in the course of the optic nerve. He found that in the bulb a strong affinity existed for the atoxyl molecule, but not for inorganic arsenic. Atoxyl amblyopia, in fact, seems to depend on neither the arsenic nor aniline constituent. Many cases of blindness have been reported after the use of arsacetin and soamin. No instance has occurred after arsenophenylglycin, but if this substance is used improperly or in unsuitable cases, affection of the vision will not improbably occur.

Some experiments made at the Liverpool School of Tropical Medicine³⁹ on the use of cold in the treatment of trypanosome infections are of interest. It may be at once stated that the published results, even in the case of animals, are inconclusive, but the experiments are

still in progress. Major Ross points out that there are indications that an abrupt transition of the host from a warm to a cold medium may influence adversely parasites which he harbours. The patient spends part of his time in the cold chamber, the temperature of which is regulated.

Time has only emphasized the inefficacy of any treatment in advanced cases; life may be prolonged, but ultimate recovery cannot be hoped for.

ALLAIN and TRAUTMANN⁴⁰ have called attention to instances in which human trypanosomiasis has appeared to be favourably influenced by an attack of pneumonia. An account is given of two cases in natives. One was that of a woman, who was under observation or treatment for four months, and then had a severe attack of pneumonia. Improvement at once set in, and she is described fourteen months later as being in excellent health. Another woman contracted pneumonia after being six weeks under observation, during which she received 5.75 gm. atoxyl. Fourteen months later she also was in good health. One gm. atoxyl was given in this case after the pneumonia, but otherwise there was no treatment. The authors rightly say that they cannot generalise from two observations, but these are suggestive.

THIROUX,⁴¹ who also has observed cases in which apparent cure occurred after quite inadequate treatment, has suggested that this is due to the presence of antibodies. The trypanosomes, he would suppose, are in a state of unstable equilibrium with the antibodies, and very small doses of trypanocides are able to disturb it in favour of the latter. He cites some cases of BRODEN and RODHAIN treated with a few injections of Loeffler's (arsenical) solution which were apparently cured. The recovery, if it be such, of some of the earlier European patients who received the simplest or the minimum of treatment might be thus explained. THIROUX's is an interesting hypothesis. It has been noted by several observers that the effect produced by the injection of a trypanocide is not directly dependent on the amount, and that in many instances the blood and glands are cleared in advanced cases more readily than in earlier ones. In the advanced cases it may be supposed that antibodies are more probably present.

PROGNOSIS.

Not long ago it was doubted whether persons infected with *Trypanosoma gambiense* ever recovered. Our knowledge was based on the statement of natives and the study of native cases, which were open to the objection that even if recovery took place re-infection could not be excluded. We have now many years' experience of the disease in Europeans, and a study of the published cases leads to the belief that recoveries almost certainly occur, and, if the nature of the disease is recognised early enough, may be not infrequent. This opinion is shared by authorities such as TODD,⁴² BRODEN,⁴³ and L. MARTIN and DARRÉ.⁴⁴ It is of course open to anyone to say now or five years hence that persons who have apparently recovered may relapse. When, however, we have a case such as that of the patient whose disease was diagnosed in 1903, and certainly existed in 1900, and who has now been in vigorous health for years, we are, I think, justified in believing that the recovery is real. At present, unfortunately, we have no certain test of cure. Even susceptible animals may fail to be infected when trypanosomes are scarce. Of thirty Europeans who have died of the disease only two survived more than three years from the discovery of trypanosomes. This suggests that patients who have survived more than three years, and are free from symptoms, have a chance of recovery. The human tissues tend to get the better of this as of all parasites. Five Europeans who have lived from $4\frac{1}{4}$ to $7\frac{1}{3}$ years since trypanosomes were found in them were in June of this year in excellent health. As far as can be ascertained 3, $3\frac{1}{2}$, $3\frac{1}{2}$, $5\frac{1}{2}$ and 7 years have passed since symptoms were observed.* The last case is the one already mentioned. It seems not improbable that the others have recovered, but it would be unwise to affirm it. What share chemo-therapy has had in the restoration to health of these Europeans it is difficult to say; the treatment which many had was both short and simple. It is possible that their infections were mild and that they would have recovered without the use of drugs, never reaching the advanced stage.

With regard to natives the records which cover the longest period are those from the Uganda camps.³⁶ These show that of eighty-nine "A" cases (persons apparently in good health) admitted during the third year, by

* I have a letter, dated August 18th, from one of these patients, in which she gives a satisfactory account of herself and two of the others.

which time one would suppose the treatment methods had been brought to a high pitch of perfection, only thirty-nine remained in that class at the year's end ; while of 300 "A" cases admitted during the second year only twenty-two could be classed the same at the end of the third. They show too that of 399 patients admitted in the first six months of the camps, ninety per cent. were dead at the end of the third year, and less than one per cent. were "thought to be probably cured." There are reasons, however, for thinking that the Uganda records form no true criterion of what treatment or treatment combined with natural resistance can accomplish. The fact that, as the three years drew on, fewer and fewer "A" cases improved goes to show that many were not really, as was supposed, recent infections, *i.e.*, that if lumbar puncture had been done, trypanosomes or an excess of cells would have been found in the cerebro-spinal fluid, and the cases would have been classed otherwise. As Dr. HODGES writes :—

It seems probable that many of the later admissions which appeared to be in the earliest stage when first admitted were not actually, but only apparently, recent infections.³⁶

In any case it is not easy to see why so very few natives of Uganda have made an apparent recovery or even survived more than three years. Of forty-two Europeans infected with trypanosomiasis fifteen survived more than three years after their disease was diagnosed, a very different percentage to that in Uganda. The difference suggests that, if we could supply the natives with the food and improved conditions of the white man, we should benefit them more than by the administration of atoxyl.

In the same report there is an account of the two Indians infected in Uganda in 1905, and believed to be free from trypanosomes since 1906 and 1907 respectively. These men appear now to be in normal health and no evidence of infection can be obtained in them.

The prospects of cases in which the later nervous symptoms have appeared remain unchanged ; with or without our present treatment all seem to end sooner or later in death.

In individual cases of trypanosomiasis marked changes in the cerebro-spinal fluid, evidenced by an excess of small lymphocytes, or by the presence of large mononuclear cells and cells with vacuoles, or by an excess of albumen are unfavourable signs. BRODEN and RODHAIN⁴⁵ have paid special attention to this subject. They have done lumbar puncture

in a large series of cases before and at various intervals after treatment. They find that after a month's treatment with atoxyl or tartar emetic the number of cells diminished in most cases, and that when these remedies were combined the effect was still more marked. With the diminution in cells was associated an improvement in the patient's state; when there was no change or an augmentation the clinical condition did not improve. The character of the cells however had to be taken into account. Persistence of mononuclear cells and cells with vacuoles, even though the small lymphocytes diminished, was of bad augury. As a rule the albumen diminished with the number of cells, not always however, and in any case not in proportion. If, however, the number of cells was normal and the albumen high, mononuclear and vacuolar cells were always to be found. L. MARTIN and DARRÉ⁴⁴ consider that a slight lymphocytosis is the rule from the outset. They do not regard the presence of trypanosomes in the cerebro-spinal fluid as necessarily of grave import, but in this opinion they have no followers. Indeed the observations of AYRES KOPKE and others seem to show very clearly the reverse. MARTIN and DARRÉ believe that when relapse occurs after a period of improvement or of apparent cure the prognosis is grave; all their patients to whom this happened died.

PROPHYLAXIS.

The broad principles of prophylaxis have been known since the discovery that *Glossina palpalis* transmits the disease. They consist either in the removal of natives, infected or not infected, from the areas haunted by the fly, or in the destruction or banishment of the fly itself. Obviously the latter is the true prophylaxis, and if it should prove that wild animals harbour the virus, it is to measures directed against the fly that we must look more and more.

A method of destroying tsetse-flies was made generally known in January last. It was devised by a Portuguese planter in the island of Principe and consists in the wearing by natives of black cloth smeared with bird-lime.¹ It is said that the flies alight on the cloth and become entangled in the bird-lime, and that large numbers have been so trapped. This method was most attractive in its simpleness as well as its apparent efficacy, but it seems probable that the mainland tsetses are less easily limed than their island relatives. In the eight months which have passed not a single success has been reported.

Mr. GERALD CAMPBELL,⁴⁶ H.M. Vice-Consul, Belgian Congo, finds that a tribe on the north bank of the Lopori river, a tributary of the Congo, is comparatively free from sleeping sickness, while another on the south bank is rapidly dying out. He attributes this to the fact that the former smear on their bodies a dye which is distasteful to tsetse-flies. This, if substantiated, affords an easy method of keeping away the carriers of infection. More information about this substance has been lately received. It consists of the leaves and fruits of a plant, specimens of which for determination I hope soon to receive. An experiment carried out with it by the Rev. A. R. RUSKIN seems to show that it is really efficacious. Another native tsetsefuge, of which an account was given to Dr. ANDREW BALFOUR, was not effective on the one occasion on which he tried it. Some experimental work with volatile oils carried out by MARSHALL and FRASER⁴⁷ in Uganda is of more value. They found that the application of citronella oil to the skin kept the flies away for about an hour, but irritation was caused. This oil was also effective when sprinkled on the clothes. Eucalyptus oil was useful, especially when an equal part of olive oil was added. The fly boys preferred eucalyptus to citronella.

The only certain way at present known of getting rid of tsetse-flies is clearing, *i.e.*, removing the vegetation which shelters them and affords opportunities for breeding. In German East Africa the attempts at clearing seem to have been more complete than elsewhere. It is the aim of the German medical authorities to rid large areas of the shore of the Victoria Nyanza and Tanganyika of *Glossina palpalis*, and where it is possible the land is brought under cultivation. This method, expensive as it may be at the outset, may prove the cheapest in the end; for the removal of native villages and the drugging of their inhabitants are at the best palliatives. Where the land cannot be brought under cultivation it is difficult to prevent the vegetation springing up again. ANDERSON has suggested a method which should be of use in camps where there is no regular supply of labour. It is that each batch of carriers, before leaving, should beat flat the young vegetation over the cleared area. It is obvious that if this is done at short intervals no growth of consequence can take place.

The investigations of MARSHALL and FRASER⁴⁸ into the breeding grounds of *Glossina palpalis* not only have been the means of supplying

a large number of laboratory-bred flies for the experiments of the Sleeping Sickness Commission, but also give hope that some effective method may be discovered of controlling the multiplication of the fly. They find that on the shore of the Victoria Nyanza the flies pupate chiefly in sand, and that not much shade is required. The pupæ can be found in large numbers; on one occasion 7,000 were brought by the fly boys.

Some interesting observations of the Sleeping Sickness Commission⁴⁹ on the food of *Glossina palpalis* are worth record, though their practical bearing is not at present evident. They found that of 220 flies the gut of 60 contained blood. This was recognisable as mammalian in twenty, as non-mammalian in nine; in two instances blood was identified as coming from monkeys. Other observations were made to determine the source of the non-mammalian blood. In twenty flies the nucleated red corpuscles were measured, and from the measurements it was deduced that in thirteen they were probably reptilian or amphibian, in seven probably avian. Hitherto no evidence had been obtained that tsetse-flies feed on birds.

Recent work on drug prophylaxis suggests that some efficient preventive may be found in that direction. MORGENROTH and HALBERSTAEDTER⁵⁰ have been studying the action of quinine when injected into mice simultaneously with the virus of Nagana. They find that when the mice are fed on quinine for a few days before the inoculation and the medication is continued afterwards no infection occurs. They do not yet know how long it is necessary to continue the quinine feeding. If the quinine was introduced under the skin it merely delayed the infection, if into the peritoneum it had no effect at all. The method should be tried with larger animals; for the mouse, owing partly to the large quantities of trypanocides it will bear, is the most easy of all mammals to treat.

I am not aware of any attempts to administer trypanocidal drugs to monkeys and other susceptible animals while they are being subjected to the bites of infected flies. This surely is a promising line of research.

APPENDIX.

Periodicity of Trypanosomes.—Before June of this year a few observations on this subject had been made, but largely owing to the crudity of the methods no definite results had been obtained. Our

PRESIDENT and Dr. DAVID THOMSON²¹ then applied a method of exact enumeration of the parasites, and thus discovered not only that a very definite periodicity exists, but that parasites are present in the peripheral blood in the negative as well as in the positive phase. Of this method we have no precise details; it is based on the thick film process of Ross, and the parasites are counted in a measured quantity of blood. A patient with sleeping sickness was thus studied for ten weeks. The result, expressed in a curve, shows that when active trypanocidal treatment was not in progress, a wave of trypanosome increase, abrupt in its ascent as in its descent, occurred every seven or eight days; the parasites at the summit of the wave numbered 300 to 1,400 per cubic millimetre, and at the depth of the trough between 10 and 50. There is an indication in the curve that a slight wave of increased temperature precedes or accompanies the wave of trypanosome increase, and it is clearly demonstrated that these last waves, while varying in height, show on the whole an alternation of relative highness and lowness. The trypanosomes were counted daily.

It is obvious as Major Ross points out that, if such counts are made regularly, the effect of particular drugs on the parasites can be accurately measured. It is possible that the phase at which the drug enters the circulation may be of importance. A trypanocide given when the number of trypanosomes was falling might have a less effect than the same given when they were rising, and in the last case the immunising stroke, as EHRLICH calls it, is likely to be much greater, because more parasites will succumb. The alternation of high and low rises may find its explanation in a partial immunity, the result of dissolution of many parasites. These observations are being continued.

The South American Trypanosomiasis.—Though the form of human trypanosomiasis discovered by CHAGAS¹³ in Brazil differs in many respects from the African disease, it deserves a short mention. It was briefly described in April of last year, but few details were available till the beginning of 1910. The parasite differs from that of sleeping sickness in two particulars: instead of multiplying by longitudinal fission in the peripheral blood, it splits up into eight merozoites within its limiting membrane in the lung capillaries and, though this seems less certain, it spends part of its life in the red corpuscle. In consequence of its mode of multiplication it has been named by Chagas

Schizotrypanum. The symptoms produced in man are similar to those of sleeping sickness, but there is no mention of lethargy or somnolence; the clinical records are at present scanty. The transmitting agent is a bug which sucks blood at night. It is the true host; for, after feeding on an infected man or animal, it is not capable of infecting another till eight days have passed, but, after that, remains infective for an indefinite period. Chagas believes that the forms which are to infect the new vertebrate leave the alimentary canal and appear in the body cavity, eventually reaching the salivary glands. At any rate there seems little doubt that trypanosome forms do appear in the body fluids. Chagas expresses the belief that only bugs which have flagellates in their salivary glands are infective, but he has brought no experimental proof; against this belief is the fact that he infected many animals by the introduction of fluid from the bug's intestine. From the result of his transmission experiments with different species of animals he concluded that the forms capable of infecting the bug develop only in certain animals; he instances a South American monkey and man. He could not infect bugs from infected guinea-pigs. No observations besides those of Chagas have been published.

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